Under 37 C.F.R. § 1.116 filed on July 28, 2002 in response to the April 9, 2003 Final Office Action **not** be entered.

The present Amendment is responsive to the Final Office Action dated April 9, 2003 and the Advisory Action dated August 13, 2003 and is accompanied by a Request for Continued Examination under 37 C.F.R. § 1.114, a courtesy copy of the pending claims, a PTO form SB-08A and an English abstract of citation number 4, DE 19501032 A1, and a Petition for Extension of Time, up to and including September 9, 2003 and its accompanying fee.

It is believed that no fee other than payment for the second month extension of time is required for these submissions. However, should the U.S. Patent and Trademark Office determine that any other fee(s) is due or that any refund is owed for this application, the Commissioner is hereby authorized and requested to charge the required fee(s) and/or credit the refund(s) owed to our Deposit Account No. 04-0100.

Amendments to the Claims are reflected in the listing of claims which begins on page 3 of this paper.

Remarks/Arguments begin on page 23 of this paper.

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

Claims 1-54 (Cancelled)

Claim 55 (Currently Amended): A transgenic non-human mammal whose genome comprises:

(a) a nucleotide sequence encoding a constitutively enzymatically active human matrix metalloproteinase that cleaves Type II collagen, wherein the nucleotide sequence encoding the metalloproteinase is operatively linked to a regulatable promoter; and

(b) a nucleotide sequence encoding a repressor-activator fusion polypeptide that binds to the regulatable promoter in the absence of a repressor-activator fusion polypeptide-binding compound and does not bind to the regulatable promoter in the presence of the compound, which nucleotide sequence encoding the repressor-activator fusion polypeptide is operatively linked to a ~~chondrocyte-tissue~~ joint-specific promoter,

wherein expression of the metalloproteinase is capable of being repressed in the mammal until adulthood, and wherein the metalloproteinase is capable of being expressed in the mammal during adulthood to a level sufficient to cause Type II collagen degradation in the joints of the mammal.

Claim 56 (Previously Presented): The transgenic mammal of claim 55, wherein the matrix metalloproteinase is selected from the group consisting of MMP-1, MMP-8, and MMP-13.

Claim 57 (Previously Presented): The transgenic mammal of claim 56, wherein the matrix metalloproteinase is MMP-13.

Claim 58 (Cancelled)

Claim 59 (Currently Amended): The transgenic mammal of claim ~~58~~ 57, wherein the MMP-13 comprises the sequence of SEQ ID NO: 1 or SEQ ID NO: 21.

Claim 60 (Previously Presented): The transgenic mammal of claim 55, wherein the repressor-activator fusion polypeptide is a chimeric tetracycline repressor-VP16 transcription activator polypeptide and the regulatable promoter is a Tn10 sequence linked to a portion of the CMV IE promoter.

Claim 61 (Previously Presented): The transgenic mammal of claim 60, wherein the regulatable promoter comprises the sequence of SEQ ID NO: 2.

Claim 62 (Previously Presented): The transgenic mammal of claim 55, wherein the Type II collagen degradation results in a loss of proteoglycan, cleavage of Type II collagen into a TC^A degradation product, a change in joint function, joint space narrowing, destruction of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, osteophyte formation, or combinations thereof.

Claim 63 (Currently Amended): The transgenic mammal of claim 55, wherein the ~~chondrocyte-tissue~~ joint-specific promoter is a Type II collagen promoter.

Claim 64 (Currently Amended): A transgenic rat whose genome comprises:

(a) a nucleotide sequence encoding a constitutively enzymatically active human matrix metalloproteinase that cleaves Type II collagen, wherein the nucleotide sequence encoding the metalloproteinase is operatively linked to a tetracycline-regulatable promoter; and

(b) a nucleotide sequence encoding a repressor-activator fusion polypeptide that binds to the tetracycline regulatable promoter in the absence of tetracycline or a tetracycline analog and does not bind to the regulatable promoter in the presence of tetracycline or tetracycline analog, which nucleotide sequence encoding the repressor-activator fusion polypeptide is operatively linked to a ~~chondrocyte tissue~~ joint-specific promoter,

wherein expression of the metalloproteinase is capable of being repressed in the rat until adulthood, and wherein the metalloproteinase is capable of being expressed in the rat during adulthood to a level sufficient to cause Type II collagen degradation in the joints of the rat.

Claim 65 (Currently Amended): The transgenic rat of claim 64, wherein the matrix metalloproteinase is constitutively enzymatically active MMP-13, the tetracycline-regulatable promoter is tet07, the repressor-activator fusion polypeptide is tTA, and the ~~chondrocyte tissue~~ joint-specific promoter is a Type II collagen promoter.

Claim 66 (Previously Presented): The transgenic rat of claim 64, wherein the Type II collagen degradation results in a loss of proteoglycan, cleavage of type II collagen into a TC^A

degradation product, a change in joint function, joint space narrowing, destruction of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, osteophyte formation, or combinations thereof.

Claim 67 (Previously Presented): A method for producing degradation of Type II collagen in the joints of a transgenic non-human mammal, which method comprises:

(a) maintaining the transgenic mammal of claim 55 in presence of the transcription activator protein-binding compound until adulthood; and

(b) activating expression of the matrix metalloproteinase in the transgenic mammal by withholding the compound from the mammal after the mammal has reached adulthood such that the matrix metalloproteinase degrades Type II collagen in the joints of the transgenic mammal.

Claim 68 (Previously Presented): The method according to claim 67, wherein the Type II collagen degradation results in a loss of proteoglycan, cleavage of type II collagen into a TC^A degradation product, a change in joint function, joint space narrowing, destruction of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, osteophyte formation, or combinations thereof.

Claim 69 (Currently Amended): A method for producing degradation of Type II collagen in the joints of a transgenic non-human mammal, which method comprises:

(a) maintaining the transgenic mammal of claim 60 in the presence of tetracycline or a tetracycline analog until adulthood; and

(b) activating expression of the matrix metalloproteinase by withholding the tetracycline or tetracycline analog from the mammal after the mammal has reached adulthood, such that the matrix metalloproteinase degrades Type II collagen in the joints of the transgenic mammal.

Claim 70 (Previously Presented): The method according to claim 69, wherein the tetracycline analog is doxycycline.

Claim 71 (Previously Presented): The method according to claim 69, wherein the Type II collagen degradation results in a loss of proteoglycan, cleavage of type II collagen into a TC^A degradation product, a change in joint function, joint space narrowing, destruction of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, osteophyte formation, or combinations thereof.

Claim 72 (Previously Presented): A method for producing degradation of Type II collagen in the joints of a transgenic rat, which method comprises

(a) maintaining the transgenic rat of claim 64 in the presence of tetracycline or a tetracycline analog until adulthood; and

(b) activating expression of the matrix metalloproteinase by withholding the tetracycline or tetracycline analog from the rat after the rat has reached adulthood, such that the matrix metalloproteinase degrades Type II collagen in the joints of the transgenic rat.

Claim 73 (Previously Presented): The method according to claim 72, wherein the tetracycline analog is doxycycline.

Claim 74 (Previously Presented): The method according to claim 72, wherein the Type II collagen degradation results in a loss of proteoglycan, cleavage of type II collagen into a TC^A degradation product, a change in joint function, joint space narrowing, destruction of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, osteophyte formation, or combinations thereof.

Claim 75 (Currently Amended): A transgenic non-human mammal whose genome comprises:

(a) a nucleotide sequence encoding a constitutively enzymatically active human matrix metalloproteinase that cleaves Type II collagen, wherein the nucleotide sequence encoding the metalloproteinase is operatively linked to a regulatable promoter; and

(b) a nucleotide sequence encoding a transcription activator protein that binds to the regulatable promoter in the presence of a transcription activator protein-binding compound and does not bind to the regulatable promoter in the absence of the compound,

which nucleotide sequence encoding the transcription activator protein is operatively linked to a ~~chondrocyte tissue~~ joint-specific promoter;

wherein expression of the metalloproteinase is capable of being repressed in the mammal until adulthood, and wherein the metalloproteinase is capable of being expressed in the mammal during adulthood to a level sufficient to cause Type II collagen degradation in the joints of the mammal.

Claim 76 (Previously Presented): The transgenic mammal of claim 75, wherein the matrix metalloproteinase is selected from the group consisting of MMP-1, MMP-8, and MMP-13.

Claim 77 (Previously Presented): The transgenic mammal of claim 76, wherein the matrix metalloproteinase is MMP-13.

Claim 78 (Cancelled)

Claim 79 (Currently Amended): The transgenic mammal of claim ~~78~~ 77, wherein the MMP-13 comprises the sequence of SEQ ID NO: 1 or SEQ ID NO: 21.

Claim 80 (Currently Amended): The transgenic mammal of claim 75, wherein the ~~chondrocyte tissue~~ joint-specific promoter is a Type II collagen promoter.

Claim 81 (Currently Amended): The transgenic mammal of claim 75, wherein the transcription activator protein is a chimeric polypeptide comprising a transactivator domain linked to an ecdysone receptor ligand-binding domain, and wherein the transgenic mammal

further comprises a nucleotide sequence encoding a retinoid X receptor (RXR), which nucleotide sequence encoding RXR is operatively linked to a ~~chondrocyte tissue~~ joint-specific promoter.

Claim 82 (Previously Presented): The transgenic mammal of claim 75, wherein the transcription activator protein is a chimeric polypeptide comprising a transactivator domain linked to a progesterone receptor ligand-binding domain.

Claim 83 (Previously Presented): The transgenic mammal of claim 75, wherein the transcription activator protein is a chimeric polypeptide comprising a transactivator domain linked to a steroid binding domain.

Claim 84 (Previously Presented): The transgenic mammal of claim 75, wherein the Type II collagen degradation results in a loss of proteoglycan, cleavage of type II collagen into a TC^A degradation product, a change in joint function, joint space narrowing, destruction of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, osteophyte formation, or combinations thereof.

Claim 85 (Previously Presented): A method for producing degradation of Type II collagen in the joints of a transgenic non-human mammal, which method comprises:

(a) maintaining the transgenic mammal of claim 75 in the absence of the transcription activator protein-binding compound until adulthood; and

(b) activating expression of the matrix metalloproteinase in the transgenic mammal by administering the compound to the mammal after the mammal has reached adulthood such that the matrix metalloproteinase degrades Type II collagen in the joints of the mammal.

Claim 86 (Previously Presented): A method for producing degradation of Type II collagen in the joints of a transgenic non-human mammal, which method comprises:

(a) maintaining the transgenic mammal of claim 81 in the absence of ecdysone, an ecdysone analog, or dexamethasone until adulthood; and

(b) activating expression of the matrix metalloproteinase in the transgenic mammal by administering ecdysone, an ecdysone analog, or dexamethasone to the mammal after the mammal has reached adulthood such that the matrix metalloproteinase degrades Type II collagen in the joints of the mammal.

Claim 87 (Previously Presented): A method for producing degradation of Type II collagen in the joints of a transgenic non-human mammal, which method comprises:

(a) maintaining the transgenic mammal of claim 82 in the absence of mifeprestone (RU 486) until adulthood; and

(b) activating expression of the matrix metalloproteinase in the transgenic mammal by administering mifepristone (RU 486) to the mammal after the mammal has reached

adulthood such that the matrix metalloproteinase degrades Type II collagen in the joints of the mammal.

Claim 88 (Previously Presented): The method according to claim 86, wherein the Type II collagen degradation results in a loss of proteoglycan, cleavage of type II collagen into a TC^A degradation product, a change in joint function, joint space narrowing, destruction of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, osteophyte formation, or combinations thereof.

Claim 89 (Previously Presented): The method according to claim 87, wherein the Type II collagen degradation results in a loss of proteoglycan, cleavage of type II collagen into a TC^A degradation product, a change in joint function, joint space narrowing, destruction of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, osteophyte formation, or combinations thereof.

Claim 90 (Currently Amended): A method for evaluating the potential of a ~~compound~~ composition to counteract degradation of Type II collagen in joints of a non-human transgenic mammal, which method comprises:

(a) administering the ~~compound~~ composition to the transgenic mammal of claim 55 in which a phenotypic change has been produced by activation of expression of the metalloproteinase ~~has been activated~~ during adulthood of the transgenic mammal, wherein the phenotypic change is selected from the group

consisting of loss of proteoglycan, cleavage of Type II collagen into a TC^A degradation product, a change in joint function, joint space narrowing, destruction of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, osteophyte formation, and combinations thereof; and

(b) comparing the extent of ~~loss of proteoglycan, cleavage of Type II collagen into a TC^A degradation product, a change in joint function, joint space narrowing, destruction of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, or osteophyte formation~~ the phenotypic change in the mammal to which the ~~compound~~ composition was administered ~~relative to~~ with that of a control transgenic mammal in which the composition was not administered but expression of the metalloproteinase was activated at the same age as it was activated in the animal in which the composition was administered ~~without administering the compound~~,

wherein any less extensive development in the nature or extent of the phenotypic change or any increased length of time required for ~~the loss of proteoglycan, cleavage of Type II collagen into a TC^A degradation product, a change in joint function, joint space narrowing, destruction of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, or osteophyte formation~~ the phenotypic change to develop in the mammal that has been administered the ~~compound~~ composition relative to the control mammal, indicates the potential

of the ~~compound~~ composition to counteract degradation of Type II collagen in joints of a mammal.

Claim 91 (Currently Amended): A method for evaluating the potential of a ~~compound~~ composition to counteract degradation of Type II collagen in joints of a non-human transgenic mammal, which method comprises:

(a) administering the ~~compound~~ composition to the transgenic mammal of claim 60 in which a phenotypic change has been produced by activation of expression of the metalloproteinase ~~has been activated~~ during adulthood of the transgenic mammal, wherein the phenotypic change is selected from the group consisting of loss of proteoglycan, cleavage of Type II collagen into a TC^A degradation product, a change in joint function, joint space narrowing, destruction of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, osteophyte formation, and combinations thereof; and

(b) comparing the extent of ~~loss of proteoglycan, cleavage of Type II collagen into a TC^A degradation product, a change in joint function, joint space narrowing, destruction of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, or osteophyte formation~~ the phenotypic change in the mammal to which the ~~compound~~ composition was administered ~~relative to~~ with that of a control transgenic mammal in which the

composition was not administered but expression of the metalloproteinase was activated at the same age as it was activated in the animal in which the composition was administered ~~without administering the compound~~,

wherein any less extensive development in the nature or extent of the phenotypic change or any increased length of time required for ~~the loss of proteoglycan, cleavage of Type II collagen into a TC^{A} degradation product, a change in joint function, joint space narrowing, destruction of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, or osteophyte formation~~ the phenotypic change to develop in the mammal that has been administered the ~~compound~~ composition relative to the control mammal, indicates the potential of the ~~compound~~ composition to counteract degradation of Type II collagen in joints of a mammal.

Claim 92 (Currently Amended): A method for evaluating the potential of a ~~compound~~ composition to counteract degradation of Type II collagen in joints of a transgenic ~~mouse or~~ rat, which method comprises:

(a) administering the ~~compound~~ composition to the transgenic ~~mammal~~ rat of claim 64 in which a phenotypic change has been produced by activation of expression of the metalloproteinase ~~has been activated~~ during adulthood of the transgenic rat, wherein the phenotypic change is selected from the group consisting of loss of proteoglycan, cleavage of Type II collagen into a TC^{A}

degradation product, a change in joint function, joint space narrowing, destruction of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, osteophyte formation, and combinations thereof; and

(b) comparing the extent of ~~loss of proteoglycan, cleavage of Type II collagen into a TC^A degradation product, a change in joint function, joint space narrowing, destruction of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, or osteophyte formation~~ the phenotypic change in the ~~mammal~~ rat to which the ~~compound~~ composition was administered ~~relative to~~ with that of a control transgenic rat ~~mammal~~ in which the composition was not administered but expression of the metalloproteinase was activated at the same age as it was activated in the animal in which the composition was administered ~~without administering the compound~~,

wherein any less extensive development in the nature or extent of the phenotypic change or any increased length of time required for ~~the loss of proteoglycan, cleavage of Type II collagen into a TC^A degradation product, a change in joint function, joint space narrowing, destruction of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, or osteophyte formation~~ the phenotypic change to develop in the ~~mammal~~ rat that has been administered the ~~compound~~ composition relative to the control ~~mammal~~ rat, indicates the potential of the ~~compound~~ composition to counteract degradation of Type II collagen in joints of a mammal.

Claim 93 (Currently Amended): A method for evaluating the potential of a ~~compound~~ composition to counteract degradation of Type II collagen in joints of a non-human transgenic mammal, which method comprises:

(a) administering the ~~compound~~ composition to the transgenic mammal of claim 75 in which a phenotypic change has been produced by activation of expression of the metalloproteinase ~~has been activated~~ during adulthood of the transgenic mammal, wherein the phenotypic change is selected from the group consisting of loss of proteoglycan, cleavage of Type II collagen into a TC^A degradation product, a change in joint function, joint space narrowing, destruction of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, osteophyte formation, and combinations thereof; and

(b) comparing the extent of ~~loss of proteoglycan, cleavage of Type II collagen into a TC^A degradation product, a change in joint function, joint space narrowing, destruction of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, or osteophyte formation~~ the phenotypic change in the mammal to which the ~~compound~~ composition was administered ~~relative to~~ with that of a control transgenic mammal in which the composition was not administered but expression of the metalloproteinase was activated at the same age as it was activated in the animal in which the composition was administered ~~without administering the compound~~,

wherein any less extensive development in the nature or extent of the phenotypic change or any increased length of time required for ~~the loss of proteoglycan, cleavage of Type II collagen into a TC^A degradation product, a change in joint function, joint space narrowing, destruction of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, or osteophyte formation~~ the phenotypic change to develop in the mammal that has been administered the ~~compound~~ composition relative to the control mammal, indicates the potential of the ~~compound~~ composition to counteract degradation of Type II collagen in joints of a mammal.

Claim 94 (Currently Amended): A method for evaluating the potential of a ~~compound~~ composition to counteract degradation of Type II collagen in joints of a non-human transgenic mammal, which method comprises:

(a) administering the ~~compound~~ composition to the transgenic mammal of claim 81 in which a phenotypic change has been produced by activation of expression of the metalloproteinase ~~has been activated~~ during adulthood of the transgenic mammal, wherein the phenotypic change is selected from the group consisting of loss of proteoglycan, cleavage of Type II collagen into a TC^A degradation product, a change in joint function, joint space narrowing, destruction of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, osteophyte formation, and combinations thereof; and

(b) comparing the extent of ~~loss of proteoglycan, cleavage of Type II collagen into a TC[A] degradation product, a change in joint function, joint space narrowing, destruction of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, or osteophyte formation~~ the phenotypic change in the mammal to which the ~~compound~~ composition was administered ~~relative to~~ with that of a control transgenic mammal in which the composition was not administered but expression of the metalloproteinase was activated at the same age as it was activated in the animal in which the composition was administered ~~without administering the compound~~,

wherein any less extensive development in the nature or extent of the phenotypic change or any increased length of time required for ~~the loss of proteoglycan, cleavage of Type II collagen into a TC[A] degradation product, a change in joint function, joint space narrowing, destruction of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, or osteophyte formation~~ the phenotypic change to develop in the mammal that has been administered the ~~compound~~ composition relative to the control mammal, indicates the potential of the ~~compound~~ composition to counteract degradation of Type II collagen in joints of a mammal.

Claim 95 (Currently Amended): A method for evaluating the potential of a ~~compound~~ composition to counteract degradation of Type II collagen in joints of a non-human transgenic mammal, which method comprises:

(a) administering the ~~compound~~ composition to the transgenic mammal of claim 82 in which a phenotypic change has been produced by activation of expression of the metalloproteinase ~~has been activated~~ during adulthood of the transgenic mammal, wherein the phenotypic change is selected from the group consisting of loss of proteoglycan, cleavage of Type II collagen into a TC^A degradation product, a change in joint function, joint space narrowing, destruction of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, osteophyte formation, and combinations thereof; and

(b) comparing the extent of ~~loss of proteoglycan, cleavage of Type II collagen into a TC^A degradation product, a change in joint function, joint space narrowing, destruction of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, or osteophyte formation~~ the phenotypic change in the mammal to which the ~~compound~~ composition was administered ~~relative to~~ with that of a control transgenic mammal in which the composition was not administered but expression of the metalloproteinase was activated at the same age as it was activated in the animal in which the composition was administered ~~without administering the compound~~,

wherein any less extensive development in the nature or extent of the phenotypic change or any increased length of time required for ~~the loss of proteoglycan, cleavage of Type II collagen into a TC^A degradation product, a change in joint function, joint space narrowing, destruction~~

~~of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, or osteophyte formation~~ the phenotypic change to develop in the mammal that has been administered the ~~compound~~ composition relative to the control mammal, indicates the potential of the ~~compound~~ composition to counteract degradation of Type II collagen in joints of a mammal.

Claim 96 (Currently Amended): A method for evaluating the potential of a ~~compound~~ composition to counteract degradation of Type II collagen in joints of a non-human transgenic mammal, which method comprises:

(a) administering the ~~compound~~ composition to the transgenic mammal of claim 83 in which a phenotypic change has been produced by activation of expression of the metalloproteinase ~~has been activated~~ during adulthood of the transgenic mammal, wherein the phenotypic change is selected from the group consisting of loss of proteoglycan, cleavage of Type II collagen into a TC^A degradation product, a change in joint function, joint space narrowing, destruction of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, osteophyte formation, and combinations thereof,; and

(b) comparing the extent of ~~loss of proteoglycan, cleavage of Type II collagen into a TC^A degradation product, a change in joint function, joint space narrowing, destruction of cartilage, a change in growth plate morphology,~~

~~fibrillation and loss of articular cartilage, or osteophyte formation~~ the phenotypic change in the mammal to which the ~~compound~~ composition was administered ~~relative to~~ with that of a control transgenic mammal in which the composition was not administered but expression of the metalloproteinase was activated at the same age as it was activated in the animal in which the composition was administered ~~without administering the compound~~,

wherein any less extensive development in the nature or extent of the phenotypic change or any increased length of time required for ~~the loss of proteoglycan, cleavage of Type II collagen into a TC^{A} degradation product, a change in joint function, joint space narrowing, destruction of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, or osteophyte formation~~ the phenotypic change to develop in the mammal that has been administered the ~~compound~~ composition relative to the control mammal, indicates the potential of the ~~compound~~ composition to counteract degradation of Type II collagen in joints of a mammal.

REMARKS/ARGUMENTS

Claims 55, 63, 64, 65, 75, 80, 81, and 90-96 have been amended. Claims 58 and 78 have been cancelled without prejudice or disclaimer. Claims 55-57, 59-77 and 79-96 remain pending upon entry of this amendment.

Claims 58 and 78 were cancelled because amendment of the claims from which they depended rendered them redundant.

Claims 55, 64 and 75 have been amended to recite that the human matrix metalloproteinase is "constitutively enzymatically active." Support for this amendment can be found throughout the specification and in particular on page 6 lines 8-10, page 8 lines 14-15, page 12 lines 5-8 and lines 13-14, page 26 lines 11-13, and in Example 1.

Claims 55, 63-65, 75, 80, and 81 have been amended to recite that the promoter is "joint-specific." Support for this amendment can be found throughout the specification and in particular on page 6 lines 15-17 and lines 18-20, page 15 line 19 - page 16 line 9, page 36 line 21 - page 37 line 1, and in Examples 4 and 5.

Claims 59 and 79 have been amended to change the claim from which they depend because the claims from which they originally depended (claims 58 and 78, respectively) have been cancelled.

Claim 69 has been amended to recite that the transgenic mammal is "non-human." Support for this amendment can be found throughout the specification, for example on page 5 line 17 and on page 23 lines 7-8, and in originally filed claim 1.

Claims 90-96 have been amended to recite a method for evaluating the potential of a composition, rather than a compound, in order to prevent confusion between the composition recited in the methods of claims 90-96 with the peptide-binding regulatory compound recited in the claims from which claims 90-96 depend (e.g. the peptide-binding compound of claim 55). Claims 90-96 have also been amended to recite that any less extensive development in the nature or extent of the phenotypic change, or any increased length of time required for the phenotypic change to develop in the mammal that has been administered the composition relative to the control mammal indicates the potential of the composition to counteract the degradation of Type II collagen. Support for these amendments can be found throughout the specification and in particular on page 20 line 13 - page 21 line 6 and in claims 25-27 as originally filed.

Claims 90-96 have also been amended to recite that the control mammal is a transgenic mammal in which the composition was not administered but expression of the metalloproteinase was activated at the same age as it was activated in the animal in which the composition was administered. Support for these amendments can be found throughout the specification and in particular on page 20 line 23 - page 21 line 2.

No new matter has been added by way of these amendments.

Information Disclosure Statement

The Examiner has stated that the Information Disclosure Statement (IDS) filed February 28, 2001 is improper because the citations are allegedly incomplete. Specifically, the Examiner has requested that the US Patents list the date, name, class and subclass, and that information for the foreign patents and publications be completed. The Examiner has also indicated that citation number 4 of the PTO Form 1449 filed with the IDS on February 28, 2001, DE 19501032 A1, has not been considered because a translation has not been provided.

This Amendment is accompanied by a PTO form SB-08A in which each of the citations that had been listed in the February 28, 2001 PTO Form 1449 are listed in complete form. As requested by the Examiner, all information has been completed for these citations. The Form SB-08A submitted herewith does not list any references not previously made of record in the February 28, 2001 PTO Form 1449.

This Amendment is also accompanied by an English abstract of citation number 4, DE 19501032 A1. It is believed that Applicants have therefore met the "concise explanation" requirement of 37 § C.F.R. 1.98. In accordance with MPEP Sections 609 and 707.05(b), it is requested that DE 19501032 A1 be given thorough consideration and that it be cited of record in the prosecution history of the present application by initialing Form SB-08A next to the document.

It is respectfully noted that each of the references cited in the Form SB-08A submitted herewith was cited in an IDS and considered by the Examiner in the parent application

U.S.S.N. 08/994,689. MPEP § 609 I A (2) requires that the Examiner consider all information which had been considered by the Office in a parent application. Thus, this Form SB-08A and the English abstract of DE 19501032 A1 are being submitted herewith solely in order to assure that these citations will be printed on the face of the patent that issues from the present application.

It is believed that the Applicants' duty to disclose information material to patentability under 37 § C.F.R. 1.56 has been met. Applicants respectfully request entry of the accompanying PTO Form SB-08 and English abstract of DE 19501032 A1 and withdrawal of the objection to the Information Disclosure Statement.

Rejections under 35 U.S.C. § 112, first paragraph- written description

Claims 55-96 have been rejected for alleged failure to fulfill the written description requirement because of the phrase "chondrocyte tissue-specific promoter." In this rejection, the Examiner states that specification and the art do not teach that the Type II collagen promoter is expressed only in chondrocytes.

The phrase "chondrocyte tissue-specific promoter" has been deleted from the claims and claims 55, 63-65, 75, 80, and 81 have been amended to recite that the promoter is "joint-specific." Joint-specific promoters are well-described and enabled by the instant application.

There is literal support in the specification for "joint-specific promoter." (See page 6 lines 15-17 and lines 18-20, page 15 line 19 - page 16 line 9, page 36 line 21 - page 37 line 1,

and Examples 4 and 5 of the specification). The specification clearly teaches that spatial control of MDE expression is achieved by the use of transcriptional promoters that direct transcription selectively in joint tissues. (See specification at page 15, lines 19-20). Such joint specific expression is clearly defined as that which produces expression in non-joint tissue of less than 10%, and preferably not at all. (*Ibid.* at lines 20-23). One source of such joint specific promoter sequences includes those derived from the collagen type II promoter. (See specification at page 16, lines 1-2). Finally, the specification teaches that such joint-specific promoter sequences may comprise one or more copies of particular sequences or sub-sequences, and that these may be in direct or inverted orientation relative to each other or the sequence being regulated. (*Ibid.* at lines 2-6).

The concept of joint-specific promoters was well-known in the art at the time of invention. As set forth in the Second Neuhold Declaration (paragraph 7; a copy of the Second Neuhold Declaration and its accompanying Exhibits (Tabs 1-9), which were originally filed in the parent case U.S.S.N. 08/994,689 on August 31, 2000, was filed as Exhibit 5 with the April 30, 2002 Amendment and Response in the instant application), the specific promoter employed to achieve tissue specific expression does not make any difference, as one of ordinary skill in the art would readily appreciate. A number of issued patents that cover transgenic animals establish tissue-specific expression is sufficiently enabled for expression of a transgene, because the actual tissue specific promoter is usually of no moment. See for example U.S. Patent Nos. 5,625,124 (claim 1: "gut epithelial cell specific promoter"); 5,880,327 (claim 1:

"a mammary-gland specific promoter"); 5,917,123 (claim 1: "a cardiac-specific regulatory region"); and 6,028,245 (claim 1: "a promoter that drives expression of the transgene in skin") (all attached as Exhibit 8 with the April 30, 2002 Amendment and Response in the instant application).

The specification clearly describes and enables the joint-specific promoters of the invention. Accordingly, it is believed that this rejection, as well as the enablement rejection to "chondrocyte tissue-specific promoter" (discussed below), has been obviated and Applicants respectfully request its withdrawal.

Rejections under 35 U.S.C. § 112, first paragraph- enablement

Claims 55-96 have been rejected for failure to fulfill the enablement requirement because the specification allegedly does not enable any metalloproteinase that cleaves Type II collagen, any chondrocyte-specific promoter, or any transgenic non-human mammal.

The Examiner has rejected claims 55-57, 60-77 and 80-96 for lack of enablement because they allegedly do not specify that the MMP is constitutively active and it would allegedly require one of ordinary skill in the art undue experimentation to determine how to control proteolytic processing so that the MMP was properly cleaved and thus active.

Applicants respectfully disagree. However, in order to advance prosecution these claims have been amended to recite that the human matrix metalloproteinase is constitutively

enzymatically active. Accordingly, it is believed that this rejection has been obviated and Applicants respectfully request its withdrawal.

The Examiner has rejected claims 55-64, 66-79 and 81-96 for alleged lack of enablement because of the phrase "chondrocyte-specific promoter." The present amendment has replaced this phrase with the phrase "joint-specific promoter" in these claims.

When making this rejection, the Examiner cites Niemann 1997 (Transg. Res. Vol. 7, p. 73-75) as evidence that an assertion made by Dr. Neuhold in her Second Declaration is incorrect, namely Dr. Neuhold's assertion that the promoter used to achieve tissue specific expression does not make a difference. Specifically, the Examiner alleges that Niemann taught that transgenic pigs made with different promoters regulating growth hormone expression caused different phenotypes (one deleterious, one compatible).

Applicants respectfully traverse this rejection. The passage pointed to by the Examiner in Niemann (p. 73 Col. 2, ¶ 2, line 12 to p. 74 Col. 1, line 4) describes the deleterious outcome of a non-tissue specific promoter (which results in deleterious systemic expression of the gene controlled by the promoter) as compared to the compatible outcome of a tissue-specific promoter (which results in beneficial muscle-specific expression of the gene controlled by the promoter). Specifically, Niemann discusses how tissue-specific expression of the transgene resulted in achievement of the desired phenotype in the transgenic pig (e.g. increased diameter of muscle fibers), but that use of a non-tissue specific promoter resulted in deleterious, systemic expression of the transgene. Thus, Niemann supports the very assertion

at issue in the Second Neuhold Declaration, namely that it is simply the use of any joint-specific promoter that is important for the desired outcome. Given the importance of tissue-specific expression of the transgene to the invention, as supported by Niemann, and the ease with which one of ordinary skill can substitute one promoter for another, it is well within the level of skill to use any joint-specific promoter in this invention, whether known or yet to be discovered. In other words, as disclosed in the application, tissue-specific expression is very important, but the exact tissue-specific promoter used to achieve it matters very little. Since any such claim would be to the transgenic animal as claimed, the term "joint-specific promoter" does not unfairly "preempt the future before it has arrived" as the Examiner suggests (see page 3 of the Final Office Action). Furthermore, this rejection unduly limits the claims because the claims are directed to a particular type of transgenic animal, which successfully employs, but is not necessarily limited to, a joint-specific promoter.

In view of these arguments and those made in the preceding section (under 112, written description), Applicants assert that a transgenic non-human mammal comprising a "joint-specific promoter" is enabled and described by the instant application. Accordingly, Applicants respectfully request withdrawal of this rejection.

The Examiner has rejected claims 55-63, 67-71, 75-91, and 93-96 for alleged lack of enablement because of the phrase "transgenic non-human mammal." When making this rejection, the Examiner cited references previously of record, namely Mullins (1990), Hammen (1990), Mullins (1989), Taurog (1988), Mullins (1996), Mullins (1993), Ebert

(1988), and Wall (1996), and two references previously not of record (Mullins 1993, Hypertension, Vol. 22, p. 630-633: herein "Mullins 1993"; and Cameron 1997, Mol. Biol. Vol. 7, p. 253-265: herein "Cameron 1997").

The Examiner cites Cameron 1997 for teaching that transgene expression is unpredictable because of the effects of genetic background and insertion site on transgene expression. The Examiner then concludes that "since mice and rats having [sic] increased genetic diversity, the unpredictability of whether the phenotype obtained in mice would occur in rats is increased." (see page 15 of the Final Office Action).

Applicants respectfully disagree and traverse this rejection. Nothing in Cameron 1997 supports the Examiner's assertion that increased genetic diversity (i.e., different species) is related to the unpredictability of transgene expression. Rather, the reference discusses the effects of the placement of the transgene with respect to the overall chromatin structure on transgene expression. Nothing in Cameron correlates diversity of chromatin structure with species-specificity. As described by Cameron, the effect of placement of the transgene with respect to overall chromatin structure is an issue relevant even within species and is not species dependent (see p. 256 col. 2 lines 3-9 of Cameron which describes that such effects are seen with transgenic mice (not between species) made with the same construct). Thus, Cameron supports Applicants' assertion that at the time of the present invention, it was routine for one skilled in the art to screen, whether the screening be done within or between species, for

transgenic animals that work, i.e., in which transgene insertion occurs at an accessible location in the chromosome.

Cameron does not correlate genetic diversity or species diversity with unpredictability of transgene expression. Rather, Cameron discloses that *all* transgene expression depends on random insertion of the transgene in a productive integration site, both within and between species, and that it is routine for one skilled in the art to test and make transgenic animals to find one with the desired phenotype.

For these reasons and the reasons previously made of record, none of the references cited by the Examiner establish lack of enablement with respect to "transgenic non-human mammals." Such animals are enabled; given the tools (in this case the MDE, regulated expression system, and tissue-specific expression system) and the mechanisms for testing (any of the indicia of collagen II degradation), it is merely routine experimentation to make and test transgenic animals to find one that works. In other words, making a transgenic animal involves the same empirical testing process as making any other biotechnological material, such as a hybridoma that produces a desired monoclonal antibody or a clone of a gene of interest. *In re Wands* the courts have acknowledged that in the field of biology a lot of experimentation can be necessary and that most attempts to achieve the experimental goal will result in failure but that as long as one can screen for successful results, such experimentation does not constitute undue experimentation (858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed.

Cir. 1988)). For example, in the instance of *In re Wands*, the court found the following process did not constitute undue experimentation:

> by screening enough clones (often hundreds at a time), hybridomas may be found that secrete antibodies against the antigen of interest. 858 F.2d at 738

The Examiner has not addressed Applicant's contention that the references cited to support lack of enablement establish the opposite proposition: each of these references show that a useful transgenic animal was created through the empirical process that enables the claimed invention. In the present Action, the Examiner has cited Mullins 1993 for teaching that integration of a transgene into a different species of animal results in divergent phenotypes. Mullins 1993 is simply a review article that summarizes references that were already of record (specifically Mullins 1990 and Hammer 1990 (see p. 631 Col. 1 end of ¶ 1 of Mullins 1993)). These references also show that, as with many experimental biological processes, creating a desired transgenic animal requires multiple trials, with screening and selection processes to select the successes. The Examiner has failed to establish any reason why the transgenic animal differs from the other biological arts, such as that discussed in *In re Wands,* in this respect.

For the reasons advanced in the Second Neuhold Declaration, the specification enables claims to non-human transgenic mammals. In particular, ". . . contrary to the examiner's assertions, as of 1996 creation of transgenic mammals required no more than ordinary technical efforts - indeed, technical efforts with shortcomings that are readily overcome"

(Neuhold Declaration, paragraph 9). All of these techniques are set forth in the specification at pages 22-26. Moreover, this clear assertion by one of ordinary skill in the art outweighs the Examiner's misunderstanding of the cited transgenic animal references.

In short, the Examiner's grounds for rejection are in error given the advanced state of the art, including general recognition of enablement of creation of transgenic animals (irrespective of whether or not such efforts are cost effective), widespread knowledge of regulatable expression systems, the understanding in the art of tissue-specific expression, and the number of well known extracellular matrix degrading enzymes from which to choose. The present invention is broadly enabled, and the Examiner has not met his burden of challenging enablement with reasonable evidence. Accordingly, the rejection under 35 U.S.C. § 112, first paragraph is in error and should be withdrawn.

Rejections under 35 U.S.C. § 112, second paragraph-indefiniteness

In the August 13, 2003 Advisory Action the Examiner stated that the proposed amendments presented in the July 28, 2002 Response and Amendment (not entered) would introduce language that would require an indefiniteness rejection. Applicants thank Examiner Wilson for this observation and note that the claims presented herewith have been revised accordingly.

Claim 90 has been rejected for alleged indefiniteness because the scope of "non-human mammal" and "transgenic mammal" on lines 2 and 4, respectively, is not commensurate. Line

2 has been amended to recite "non-human transgenic mammal." Thus, this rejection has been obviated and Applicants respectfully request its withdrawal.

Claims 90-96 have been rejected for indefiniteness because the Examiner contends that steps (a) and (b) do not make it clear when the compound is administered to the mammal relative to administering the regulatory compound, obtaining MMP expression and Type II collagen degradation. Step (a) of claims 90-96 have been amended to recite that the composition is administered to a transgenic mammal "in which a phenotypic change has been produced by activation of expression of the metalloproteinase during adulthood of the transgenic mammal." Accordingly, this rejection has been obviated and Applicants respectfully request its withdrawal.

The Examiner has also rejected claims 90-96 because step (b) of these claims is allegedly confusing and because there is allegedly no antecedent basis for the phrase "the extent of..." because the listed phenotypes are not required in step (a) or in the parent claims. Claims 90-96 have been amended to provide antecedent basis for the phrase "the extent of phenotypic change" in step (b) of the claims by specifying in step (a) of the claims that phenotypic changes occur (e.g. loss of proteoglycan, cleavage of Type II collagen into a TC^A degradation product, a change in joint function, joint space narrowing, destruction of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, osteophyte formation, and combinations thereof) in the transgenic animal. Accordingly, these rejections have been obviated and Applicants respectfully request their withdrawal.

The Examiner has also rejected claims 90-96 for alleged indefiniteness because the metes and bounds of the control animal are unclear. The Examiner has also inquired as to whether the control animal is transgenic.

Claims 90-96 have been amended to recite that the control animal is "transgenic." In addition, these claims have been amended to recite that the control transgenic mammal is one "in which the composition was not administered but expression of the metalloproteinase was activated at the same age as it was activated in the animal in which the composition was administered." Page 20 line 23 - page 21 line 2 of specification also clearly describes the metes and bounds of a control animal:

> Control animals comprise age- and sex-matched transgenic animals that are maintained under an identical regimen (i.e. express the transgenes) but which do not receive the composition.

Thus, it is believed that this rejection has been obviated and Applicants respectfully request its withdrawal.

Claims 90-96 were rejected for alleged indefiniteness because the Examiner found it unclear how to determine the "difference" in a phenotypic "change" and whether the test requires comparing the development of the phenotypes listed in both test and control mammals, comparing a characteristic over a period of time, or comparing a characteristic at a specific time in the test and control animals.

Claims 90-96 have been amended to clarify that any less extensive development in the nature or extent of the phenotypic change (i.e., comparing the phenotype in the test and control

animal after the same time period), or any increased length of time required for the phenotypic change to develop in the mammal (i.e., comparing the length of time the test and control animals each take to get to a particular phenotype) that has been administered the composition relative to the control mammal indicates the potential of the composition to counteract the degradation of type II collagen. In either case, one compares the change in a test animal to that in a control, i.e., one is comparing the difference between two changed values. From this comparison one can characterize the activity of the test composition. Accordingly, Applicants respectfully request withdrawal of this rejection.

Lastly, the Examiner has rejected claims 90-96 for alleged indefiniteness because he believes the claim states that any "change" indicates the composition may counteract osteoarthritis.

As amended the claims recite "wherein any less extensive development in the nature or extent of the phenotypic change or any increased length of time required for the phenotypic change to develop in the mammal that has been administered the composition relative to the control mammal, indicates the potential of the composition to counteract the degradation of Type II collagen in the joints of the mammal." Thus, the claims do not indicate that any change indicates the composition might counteract the degradation of type II collagen. Rather, the claims indicate that any less extensive development in the nature or extent of the phenotypic change or any increased length of time required for the phenotypic change to develop in the animal indicates the potential of the composition to counteract the degradation of

Type II collagen (emphasis added). The utility of the invention lies in that this model system permits identification of lead compositions that may be useful to treat osteoarthritis. Thus, it is believed that these rejections have been obviated and Applicants respectfully request their withdrawal.

Conclusion

In view of the above amendments and remarks, it is respectfully requested that the application be reconsidered and that all pending claims be allowed and the case passed to issue.

If there are any other issues remaining which the Examiner believes could be resolved through either a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below.

Respectfully submitted,

By: 

Heather Morehouse Ettinger, Ph.D.
Reg. No. 51,658
Attorney for Applicants

Dated: September 9, 2003

Darby & Darby P.C.
Post Office Box 5257
New York, NY 10150-5257
212-527-7700